IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: MacLeod, C.L.	§	**ART UNIT: 1635**
FILED: January 27, 1999	§	**EXAMINER: A. Wang**
SERIAL NO.: 09/238,972	§	
FOR: Inhibition of Cationic Amino Acid Transporter and Uses Thereof	§	**DOCKET: D5232CIP3**

The Assistant Commissioner of Patents and Trademarks
Box NON-FEE AMENDMENT
Washington, DC 20231

RESPONSE UNDER 37 CFR 1.111

Dear Sir:

Responsive to the Office Action mailed April 13, 1999, please enter the following amendments and remarks. Reconsideration of this application as amended is respectfully requested.

REMARKS

Restriction Requirement under 35 USC §121

Responsive to the Restriction Requirement contained within the Office Action mailed April 13, 1999 for the above-

referenced application, Applicant hereby provisionally elects Group I, claims 1-9, 16, and 17 for examination, with traverse.

Applicant hereby traverses the Restriction Requirement. The Examiner maintains that claims 1-9, 16, and 17 restricted to Group I, claims 10- 15 restricted to Group II, and claims 18-20 restricted to Group III are unrelated because they are not disclosed as capable of use together and have different modes of operation, functions and effects. The Examiner's statement notwithstanding, Applicant disagrees that these constitute different inventions. The present invention teaches methods of inhibition of cationic amino acid transporter protein. All three groups disclose methods of regulating the expression of this protein. Thus, the Applicant respectfully submits that a single inventive concept is intimately intertwined between Groups I, II, and III. Therefore, it would not unduly burden the examiner to perform a search encompassing claims 1-20. For this reason, the Applicant respectfully requests that the Restriction requirement under 35 U.S.C. §121 be withdrawn.

Priority Status

Applicant's priority claim to application 08/187,634, which is a CIP of 07/686,322, which is a CIP of 07/509,684 has not

been granted because the Examiner found no support for antisense oligonucleotides in parent application 08/187,634, now U.S. Patent 5,866,123. The Applicant respectfully disagrees.

U.S. Patent 5,866,123 (Application 08/187,634) makes reference to Maniatis *et al.*, Molecular Cloning a Laboratory Manual, Cold Spring Harbor, N.Y., 1983 in column 7, lines 43-45. Maniatis *et al.*, teaches molecular biology techniques including antisense technology. Therefore, even though U.S. Patent 5,866,123 (Application 08/187,634) incorporated antisense methods by reference. U.S. Patent 5,866,123 (Application 08/187,634) claims priority to 07/686,322 (now U.S. Patent 5,312,733) which discusses antisense oligonucleotides on the paragraph bridges columns 3 and 4 of the issued patent. U.S. Patent 5,312,733 (07/686,322) claims priority to application 07/509,684, now abandoned, which also discuses antisense oligonucleotides. Therefore, the Applicant respectfully requests that claims 1-9, 16 and 17 be granted priority to the April 13, 1990 filing date of U.S. Patent Application Ser. No. 07/509,684.

The 35 USC §102 Rejection

Claims 3, 16, and 17 have been rejected under 35 USC §102(b) as being anticipated by U.S. Patent No. **5,312,733**. This rejection is respectfully traversed.

The current application is a continuation in part of U.S. Patent Application Ser. No. 08/187,634, now U.S. Patent **5,866,123** which is a continuation in part of U.S. Patent Application Ser No. 07/686,322, now U.S. Patent **5,312,733** which is a continuation in part of U.S. Patent Application Ser No. 07/509,684, As described above, the Examiner did not extend priority to 07/509,684, because U.S. Patent because 08/187,634, now U.S. Patent **5,866,123**. However, as described above, U.S. Patent **5,866,123** makes reference to **Maniatis** *et al.,* Molecular Cloning a Laboratory Manual, Cold Spring Harbor, N.Y., 1983 which teaches antisense technology. Therefore, **5,866,123** (Application 08/187,634) incorporates antisense techniques by reference. Therefore, the Applicant argues that the instant application does properly claim priority to an beyond U.S. Patent Application 07/686,322, now U.S. Patent **5,312,733**.

The 35 USC §112 Rejections

Claims 2 and 16 have been rejected under 35 USC §112, first paragraph, as "containing subject matter which was not described in the specification in such a way as convey to one skilled in the art that the inventor... had possession of the claimed invention." This rejection is respectfully traversed.

The Examiner argues that the "invention of [claims 2 and 16] is drawn to any antisense oligo which inhibits CAT2 translation and pharmaceutical compositions comprising said antisense oligo." Actually, claims 2 is directed to the oligonucleotide encoded by SEQ ID No. 2 for which the specification shows that administration in Xenopus oocytes restores L-arginine transport to normal levels. Claim 16 as well as claim 1 are directed to any oligonucleotide against CAT2 mRNA. Neither claim 2 nor claim 16 is directed toward a pharmaceutical composition. Claim 3 is directed to a pharmaceutical composition.

Nevertheless, the Applicant respectfully disagrees with the Examiner's assertion that the Applicant was not in possession of the invention at the time of filing. While unexpected difficulties can develop in the application of antisense technology, there is a broad body of literature supporting the ability of antisense technology to

down regulate gene expression. The Examiner argues that primary structure is not the sole determinant of antisense function. However, it is the major determinant. Antisense inhibition can function by a number of mechanisms including blocking ribosome binding sites, preventing ribosome progression down the mRNA strand, and stimulation of RNAse H degradation of the mRNA. Therefore, it is highly likely that a given antisense sequence will have a least some effect on the expression of a given gene. The fact that the one oligonucleotide used was able to down regulate CAT2 expression is strong evidence that other CAT2 antisense oligonucleotides will have similar effects.

As to the argument that a pharmaceutical composition is not enabled, claim 3 specifically states that the composition consists of the antisense oligonucleotide and a physiological acceptable carrier. On Page 29, lines 9-10 of the specification, the instant application mentions "liposomes or various viral vectors" as possible carriers. Further physiological carriers are well known to those skilled in the art.

Based upon the fact that claim 2 is limited to the antisense oligonucleotide of SEQ ID No. 2, Applicant respectfully requests that the 35 USC §112 rejection of claims 2 be withdrawn.

Likewise, applicant feels that the success with this antisense oligonucleotide described in the specification provides a person having ordinary skill in this art with a reasonable expectation of successfully producing other anti-CAT2 oligonucleotides. Accordingly, Applicant respectfully requests that the 35 USC §112 rejection of claim 16 be withdrawn

Claims 1-9 and 16 have been rejected under 35 USC §112, first paragraph because the specification is "only enabling for claims limited to an antisense oligo consisting of SEQ ID No: 2 and a method of inhibiting CAT2 expression using said antisense oligonucleotide." The Examiner also argues that no specific guidance is provided for application of the instant invention to any particular disease condition. This rejection is respectfully traversed.

The Examiner argues that the specification does not provide any guidance regarding administration of "any type antisense oligo targeted to CAT2 that would result in an ameliorative effect of any particular pathological state ... [or] pathological condition by inhibiting CAT2." Applicant respectfully disagrees.

The disease states listed in claims 6-9 are all diseases characterized by undesirable levels of nitric oxide. CAT2 is involved in the regulation of cellular levels of arginine which is the precursor

for nitric oxide production. Thus, regulation of CAT2 expression would be desirable for the reduction of nitric oxide levels in the listed disease conditions. Therefore, while no guidance is given for a specific disease condition, the applicability of the instant invention to these diseases would be obvious to one skilled in the art. Furthermore, since the oligo encoded by SEQ ID No. 2 downregulated arginine transport, it provides an example of an antisense oligo which would prove effective in the treatment of a pathological condition.

The Applicant disagrees that careful screening of oligonucleotides targeted to different sites may fail to identify such sites. The Examiner cites **Hoke** et al. (U.S. Patent 5,585,479, December 17, 1996) to bolster this argument and further states that the success of sites only a few nucleotides apart may vary. However, of 22 antisense oligonucleotides designed by **Hoke** et al., 12 (55%) were successful enough to include in the claims of the Patent. The Applicant asserts that this is a reasonable level of success, rebutting the Examiner's arguments that the design of other successful antisense oligonucleotides in the instant invention would be difficult.

The Examiner also cites **Gerwitz** et al. (Proc. Natl. Acad. Sci. U.S.A., 93:31613163, 1996) and **Branch** (TIBS, 23:45-50, 1998)

as teaching that the inhibitory activity of an antisense oligo depends on an unpredictable combination of sequence and structure. However, the 55% success rate of **Hoke** et al. suggests that it not unpredictable or even difficult.

The Examiner also argues that the clinical application of antisense oligonucleotides is questioned since there are several obstacles that must be overcome such as degradation, molecular size and charge, bioavailability, and toxicity. The instant application does not claim to solve all problems with antisense technology. However, results with the antisense oligonucleotide of SEQ ID No. 2 in the instant application have demonstrated that an antisense approach is a viable approach to the regulation of CAT2 expression and activity. The Examiner cites **Rojanasakul** (*Advanced Drug Delivery Reviews*, 18:115-131, 1996) regarding a case of toxicity in antisense therapy. While this case of toxicity may indicate potential problems, it is not necessarily true that toxicity will be a problem in the instant invention. As pointed out on page 46, column 2 of **Branch** et al., "all drugs are dirty" and have unintended consequences. However, these side effects do not invalidate the inventive concept behind the intended use of the claimed oligonucleotides.

The Applicant acknowledges that antisense therapy is not a refined science. However, the applicant has demonstrated that antisense manipulation of CAT2 works in a cell line. Accordingly. the Applicant respectfully requests that the 35 USC §112 rejection of claims 1-9 and 16 be withdrawn.

This is intended to be a complete response to the Office Action mailed April 13, 1999. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: May 27, 1999

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Assistant Commissioner of Patents
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CERTIFICATE OF MAILING UNDER 37 CFR 1.8

Dear Sir:

I hereby certify under 37 CFR 1.8 that the following correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to Commissioner of Patents and Trademarks, Washington DC 20231.

1) Response to Office Action (10 pages); and,
2) Return postcard.

Please return the enclosed postcard acknowledging receipt of this correspondence.

Respectfully submitted,

Date: May 27, 1999

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